The State-of-the-Art Treatment of Non-small Cell Lung Cancer

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Introduction

Lung cancer has been a major health problem worldwide, accounting for a global incidence of 1.2 million new cases yearly and a staggering mortality of 1.1 million deaths in 2001.1 In Hong Kong, lung cancer has remained the commonest malignancy in men and the third commonest in women, with a total of 4,135 new cases in 2005. Being the commonest cancer killer in both sexes, there were 3,686 deaths in the same year (Hong Kong Cancer Registry). The majority (>80%) of the lung cancers is non-small cell carcinoma (NSCLC), which is predominantly in advanced or metastatic stages upon presentation. The high mortality is mainly ascribed to disease recurrence after curative lung resection and the lack of effective treatment for advanced disease. The overall treatment plan for NSCLC largely depends on clinical staging: curative lung resection for early stages (mainly stage I and II), combined with chemoradiotherapy for locally advanced stages (mainly stage III), and systemic platinum-based chemotherapy for advanced metastatic stages (mainly stage IIIB and IV). Building on this framework of treatment strategies, there have been significant advances in the overall treatment for NSCLC over the past 5 years, especially with the emergence of targeted therapy. This review serves to highlight the important advances on the latest pharmacological treatment for NSCLC.

Adjuvant Chemotherapy for Resectable NSCLC

The staging system of NSCLC is based on the extent of involvement of primary tumour (T), regional lymph nodes (N) and distant metastases (M).2 Early resectable stages often refer to stage I or II and selected stage IIIA with either ipsilateral microscopic mediastinal lymph node involvement or chest wall invasion. The current standard treatment for early disease is still complete surgical resection, unless medically contraindicated. However, the 5-year survival rate of resected early-stage disease is still suboptimal, mainly due to presence of micrometastases leading to subsequent recurrence in distant sites.3 Therefore the use of adjuvant chemotherapy after lung resection appears to be the logical step to improve outcome. As early as in 1995, a meta-analysis from the Non-small Cell Lung Cancer Collaborative Group already suggested a slight survival benefit, though statistically insignificant, with the use of post-operative cisplatin-based chemotherapy.4 More recently, there have been several large-scale randomised controlled trials reporting on adjuvant chemotherapy in over 4,000 patients with early-stage NSCLC.5-8 In the largest randomised controlled trial reported so far on adjuvant chemotherapy, the International Adjuvant Lung Cancer Trial (IALT),9 there were 1,867 patients with stages I to III NSCLC recruited into either postoperative chemotherapy (cisplatin combined with etoposide, vinorelbine, vinblastine, or vindesine) or no adjuvant chemotherapy. After a median follow-up of 56 months, the overall survival was significantly prolonged in the chemotherapy arm, with a 4.1% absolute survival benefit at 5 years and 14% relative reduction in risk of death (HR 0.86, 95% CI 0.76-0.98, p<0.03). This was also accompanied by an improved disease-free survival with postoperative chemotherapy (HR 0.83, 95% CI 0.74-0.94, p<0.003). The reported toxicity profile was generally well tolerated. Furthermore, a pooled analysis of the recent major randomised trials (the aforementioned 4 trials5-8 and the Big Lung Trial9) suggested significant survival benefit with adjuvant chemotherapy compared to surgery alone, with a 5-year absolute benefit of 5.4%.10 The survival benefit was largely limited to resectable stage II and III disease only. Therefore, especially in younger patients with good performance status after curative resection for early-stage II or IIIA NSCLC, adjuvant cisplatin-based chemotherapy can be considered as part of the current standard practice, though there is still controversy about the optimal regimen and schedule.

Newer Agents for Treatment of Advanced or Metastatic NSCLC

Although surgery can offer the best chance of cure for lung cancer, it is unfortunately only feasible for a minority of patients, in which there is no regional involvement of mediastinal lymph nodes, pleural or pericardial malignant effusion, or distant metastases. In the presence of extensive mediastinal lymphadenopathy and locally advanced disease, the current standard treatment is combined systemic chemotherapy and radiotherapy, either given in concurrent (preferred) or sequential manner.11, 12 Over the years, systemic chemotherapy has become the standard first-line treatment for those with malignant effusion or distant metastases.13 In such patients with good performance status, a combination of platinum (cisplatin or carboplatin) and a newer generation chemotherapeutic agent (e.g. paclitaxel, docetaxel or gemcitabine) has been demonstrated to improve overall...
survival, disease-free survival and quality of life compared to best supportive care alone or older generation chemotherapy combinations in the first-line setting. The overall international experience, however, showed that the improvement in survival is modest (around 2 months prolongation of median survival compared to best supportive care alone) and the time to disease progression is usually within a few months since commencement of chemotherapy. Upon disease progression after first-line treatment, docetaxel as second-line monotherapy has been shown to have survival advantage over best supportive care alone or alternative chemotherapy, although the improvement is fairly modest at the expense of significant toxicity. Therefore there have been continued efforts looking for novel agents in the treatment of advanced or metastatic NSCLC.

**Anti-angiogenesis agents in combination with chemotherapy as first-line**

It has long been recognised that angiogenesis, regulated by proangiogenic and antiangiogenic factors, plays a crucial role in tumour growth and development of distant metastases. One of the most important proangiogenic factors involved in tumour angiogenesis is vascular endothelial growth factor (VEGF), which serves as the main target for antiangiogenic therapy in NSCLC. Bevacizumab (Avastin™) is an anti-VEGF recombinant humanised monoclonal antibody, which blocks the binding of VEGF to its receptors and subsequent downstream biologic activities. A randomised phase II study of bevacizumab in combination with carboplatin and paclitaxel or same chemotherapy alone as first-line treatment in patients with stage IIIIB or IV NSCLC has demonstrated superior response rate, time to progression and survival in the bevacizumab combination arm, but with increased risk of life-threatening haemoptysis in squamous cell carcinoma (a sub-type of NSCLC).

As a result, a recent randomised phase III study (E4599) was conducted comparing the combination of bevacizumab with chemotherapy (carboplatin and paclitaxel) versus chemotherapy alone in the treatment of advanced chemonaive non-squamous NSCLC. For the first time in phase III setting, this study has demonstrated a statistically significant survival benefit favouring the bevacizumab combination arm compared to the standard chemotherapy alone (median survival 12.3 months vs 10.3 months in bevacizumab combination vs chemotherapy alone arms, hazard ratio 0.79, p=0.003). The major toxicity appeared to be related to bleeding complications, in which the 5 deaths due to haemoptysis were exclusively from bevacizumab arm. A similarly designed phase III clinical trial on the combination of bevacizumab (at 2 doses) with chemotherapy (gemcitabine and cisplatin) has been conducted with demonstrable improvement in progression-free survival with the bevacizumab combination arm in preliminary analysis. However, this study was not designed to look into overall survival as the primary outcome. Overall, the approach in combining bevacizumab with standard platinum-based doublet chemotherapy is feasible and beneficial, at the expense of greater degree of toxicities (e.g. hypertension, proteinuria, bleeding) and cost. Ongoing studies will hopefully address the remaining controversies related to this approach, like treatment for selected squamous cell carcinoma and brain metastases.

**Pemetrexed as Second-Line Chemotherapy**

With the current standard first-line chemotherapy treatment for advanced NSCLC, tumour response is expected to be transient with disease progression mostly occurring within a few months after cessation of chemotherapy.

Pemetrexed (Alimta™) is a novel multitargeted antifolate chemotherapy that has been shown to be active against NSCLC, which acts by inhibiting the three key enzymes in pyrimidine and purine synthesis. A recent randomised phase III trial comparing pemetrexed (with vitamin B12 and folate supplementation) versus docetaxel as monotherapy second-line treatment in advanced NSCLC has demonstrated similar median progression-free survival (2.9 months for each arm) and median survival (8.3 vs 7.9 months for pemetrexed vs docetaxel). Importantly, pemetrexed chemotherapy was associated with significantly less severe neutropenia, febrile neutropenia, neutropenia with infections, and hospitalisations for neutropenic fever compared with docetaxel. Based on this study, pemetrexed has been widely approved as second-line treatment for advanced NSCLC, equally effective as docetaxel but with more favourable toxicity profile.

**Pemetrexed and Cisplatin as First-Line Chemotherapy for Adenocarcinoma**

Pathologically, non-small cell carcinoma comprises of squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Traditionally, the pharmacological treatment for different subtypes of NSCLC is similar, i.e. no particular predilection for certain chemotherapy based on cell type. A recent phase III study was conducted to compare the clinical efficacy of pemetrexed/cisplatin with gemcitabine/cisplatin as first-line treatment for advanced NSCLC. Apart from demonstrating non-inferior overall survival for the two chemotherapy regimens (median survival 10.3 months for both), pemetrexed/cisplatin entailed statistically superior survival vs gemcitabine/cisplatin among patients with adenocarcinoma (12.6 vs 10.9 months respectively) and large cell carcinoma (10.4 vs 6.7 months respectively). In contrast, the opposite finding of survival superiority with gemcitabine/cisplatin compared to pemetrexed/cisplatin in squamous cell carcinoma (10.8 vs 9.4 months respectively) was observed. This finding could be biologically plausible in light of the higher gene and protein expression of thymidylate synthase in squamous cell carcinoma compared with adenocarcinoma, thus making adenocarcinoma more prone to the anti-folate action (with thymidylate synthase as one of the key targets) of pemetrexed.

**Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI)**

In recent years, the concept of molecularly targeted therapy has evolved rapidly in the management of advanced NSCLC, which is best exemplified by the inhibition of EGFR pathway. Unlike conventional cytotoxic agents leading to non-specific cell damage or death, this class of novel agent targets specifically at the critical and unique pathway involved in tumourigenesis. The EGFR forms part of the signalling pathway that regulates tumour cell proliferation, invasion,
angio genesis, metastasis, and apoptosis. Since overexpression of EGFR is commonly found in NSCLC, various novel agents that inhibit EGFR pathway have been developed for the treatment of this neoplasm. Apart from the use of monoclonal antibody that targets the EGFR extracellular binding site, small molecules that target the intracellular adenosine triphosphate (ATP) binding site of EGFR tyrosine kinase have been studied extensively. There are two clinically available EGFR TKIs, namely gefitinib (Iressa™) and erlotinib (Tarceva™), in which the readers are recommended to refer to a recent review for more details in The Hong Kong Medical Daily in August 2008. Overall, there are phase III data to support the clinical efficacy of either gefitinib (INTEREST trial) or erlotinib as a single agent in the treatment of advanced NSCLC in the second- or third-line settings. The toxicity profile of EGFR TKI is rather different from that of systemic chemotherapy, in which the adverse effects of EGFR TKI are mostly skin reaction (dryness, pustular rash, paronychia), diarrhoea, and rarely interstitial pneumonitis. There have been several clinical (female, Asian descent, never smokers, adenocarcinoma) and molecular (EGFR gene mutations, EGFR gene copy number) predicting factors for response to treatment by EGFR TKI, though the relative importance of each of the factors is not completely elucidated. Future research will also help to define better the role of EGFR TKI in other clinical settings especially as first-line treatment in an enriched population with anticipated favourable response to this class of medications.

**Novel Treatments on the Horizon**

Besides the various advances in drug treatment as highlighted above, there have been concerted efforts worldwide in the development of novel targeted agents in the battle against NSCLC. In the years to come, we will be hearing more and more about alternative anti-angiogenesis agents with small molecules (VEGFR TKI), newer targets (like specific inhibitors of EGFR downstream signalling pathway), multi-targeted kinase inhibitors (combined VEGF and EGFR inhibitors), and monoclonal antibody targeting EGFR (like combination of cetuximab (an anti-EGFR) with chemotherapy).

**The State-of-the-Art Treatment Algorithm**

With the aforementioned new armamentaria in the treatment of NSCLC, a suggested treatment algorithm is shown in Table 1.

<table>
<thead>
<tr>
<th>Stage</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Surgery + adjuvant cisplatin-based chemotherapy (especially in patients with good performance status)</td>
<td></td>
</tr>
<tr>
<td>IIIA-IBB (non-effusion)</td>
<td>Surgery for selected resectable stage IIIA (non-effusion)</td>
<td></td>
</tr>
<tr>
<td>IIIIB (effusion-IV)</td>
<td>Combination of cisplatin-based chemotherapy and thoracic RT for non-resectable stages (concurrent more effective than sequential)</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>Options: Cisplatin-based chemotherapy (doublet) Bevacizumab combined with cisplatin-based doublet chemotherapy (non-squamous NSCLC) EGFR TKI</td>
<td>Options: Pemetrexed EGFR TKI</td>
</tr>
</tbody>
</table>

RT, radiotherapy; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor

**References**